Helicobacter pylori and Chronic ITP

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Eradication of *Helicobacter pylori* infection has been variably associated with a platelet response in patients with immune thrombocytopenic purpura (ITP). Responses occur in approximately half of ITP patients infected with this bacterium, more frequently in Japan and Italy than in other countries. For those with severe ITP (platelet count < 30×10^9/L) and a long duration of disease, eradication therapy seems to be less effective. Despite extensive efforts, distinctive clinical features and factors predicting the response to eradication therapy have not been consistently identified.

There is no established mechanism to explain how *H pylori* could be implicated in the pathogenesis of an immune-mediated platelet destruction. Several theories have been proposed to explain the platelet response to anti–*H pylori* therapy, including molecular mimicry, platelet aggregation, and the induction of a Th1 phenotype that favors the onset and/or persistence of ITP. The role of bacterium-related factors, such as the CagA (cytotoxin-associated gene A) protein, are still under investigation.

Eradication therapy is simple and inexpensive, with limited toxicity and the advantage of avoiding long-term immunosuppressive treatment for those who respond. Although the evidence and follow-up are limited, it appears reasonable to routinely screen patients with ITP for *H pylori*, particularly in those populations with a high background prevalence of *H pylori* infection.

Introduction

Helicobacter pylori is a Gram-negative microaerophilic bacterium that colonizes the human stomach of more than 50% of the world population. It is recognized as the causative agent of active chronic gastritis and is the predominant cause of peptic ulceration, i.e., gastric and duodenal ulcers.[1] Additionally, *H pylori* is a cofactor in the development of both adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphomas, and therefore has been designated as a class I carcinogen by the World Health Organization. The relationship between *H pylori* infection and idiopathic thrombocytopenic purpura (ITP) is less clear. Eradication of the infection has been reported to produce an increase of the platelet count in some studies, whereas other reports have failed to demonstrate such beneficial effects. In this review we will briefly summarize the current evidence linking *H pylori* infection to ITP, and will provide practical guidelines for *H pylori* infection detection and management.

Methods of *H pylori* Detection

H pylori can be readily detected at endoscopy by histology, culture or urease tests. Non-invasive methods for *H pylori* detection are generally used for the screening of patients who do not require direct examination of gastric mucosa and when obtaining biopsies is troublesome (e.g., bleeding ulcers, anticoagulant therapy, severe thrombocytopenia). Each detection method has strong and weak points and the methods differ in accuracy. Among the non-invasive methods, the ^{13}C-urea breath test and antigen detection in stools are considered to be the most accurate, with both sensitivity and specificity in the range of 90% to 95%.[2] Serum antibody assays have the lowest cost per correct diagnosis, but their overall accuracy is lower (sensitivity and specificity: 80% to 95%).[2] Furthermore, serology is not a specific indicator of active infection and, since antibody titers fall only slowly after successful eradication, cannot be used to determine *H pylori* eradication or to detect reinfection. Although the accuracy and reliability of assays can be improved by combined use of several methods, it is difficult and unrealistic to use all of the methods to attain a diagnosis.

Epidemiology of *H pylori* Infection in ITP

The prevalence of *H pylori* infection in adult ITP patients has been systematically reviewed and was not found different from that reported in the general healthy population matched for age and geographical area.[3] The detection method in these studies was the ^{13}C-urea breath test. Most studies were conducted in Italy, where the *H pylori* rate in the middle-aged adult general population is nearly 50%,[4] or Japan, where the prevalence of the infection is greater than 70%.[5] A low prevalence of *H pylori* infection (22%) was found in 74 North American patients,[6] which was not dissimilar from that observed in a healthy American Caucasian population.[7] Using serological tests, Michel et al

also recorded a low prevalence (29%) of *H pylori* infection in 51 adult ITP patients of white French origin; the same rate of infection was found in control subjects.[8] Conversely, a study from Colombia has reported a very high prevalence of *H pylori* infection in patients with ITP (90.6%), that was significantly different from that of control individuals (43.8%).[9]

The prevalence of *H pylori* in children with ITP also varies widely among different populations. *H pylori* infection was not detected in any of 17 pediatric patients with ITP in a Finnish population.[10] In contrast, 11 of 35 (31%) Turkish children were shown to have a *H pylori* infection as documented by a positive ^{13}C-urea breath test.[11] A study from Japan reported the presence of *H pylori* infection in 2 of 10 (20%) children.[12] *H pylori* infection was detected in 9 of 22 (41%) Chinese children from Northern Taiwan.[13] In general, the impression from the few studies in childhood ITP is that the prevalence of *H pylori* infection is higher in countries where the background prevalence of the infection is higher. This is consistent with epidemiological data suggesting that *H pylori* infection is mainly acquired in early childhood.[2]

Pathogenesis of *H pylori* Infection

H pylori infection is determined by some basic characteristics of the bacterium: urease, flagella, and adhesins.[14] In addition, virulence factors of *H pylori* such as CagA and VacA play specific roles in the primary colonization and infection. The Cag pathogenicity island (a common gene sequence believed responsible for pathogenesis) contains over 40 genes, part of which code for a complex type IV secretion system. This pathogenicity island is usually absent from *H pylori* strains isolated from humans who are carriers of *H pylori* but remain asymptomatic. The CagA protein is frequently co-expressed with VacA, a vacuolating cytotoxin.

A number of other virulence factors have been identified, which have the potential to modulate the host immune response. T cells are generally hyporesponsive during *H pylori* infection, and the existent response is polarized toward a T helper 1 (Th1) response. This type of response may be induced by *H pylori* neutrophil-activating protein (HP-NAP) and the cell wall lipopolysaccharide (LPS). HP-NAP is a dodecameric protein of 150 kDa, with a structure similar to that of bacterioferritin, that attracts and activates neutrophils, and promotes their endothelial adhesion and the production of oxygen radicals and chemokines. HP-NAP can shift antigen-specific T-cell responses from a predominant Th2 to a polarized Th1 phenotype, characterized by high levels of interferon-γ and tumor necrosis factor-α production.[15] The lipopolysaccharide (LPS) of *H pylori* shows certain blood group antigens such as Leb, Lex, Ley, and H-type I. Such antigens are thought to be involved in the adhesive process of the germ. LPS has been shown to promote Th1 type immune response in immunized BALB/c mice that may aid in the protection or clearance of *H pylori* infection.[16]

Potential Mechanisms of *H pylori*–Induced Thrombocytopenia

Many hypotheses have been advanced about the mechanisms by which *H pylori* may cause ITP (**Figure 1**; see Color Figures, page 501). One of them is molecular mimicry, according to which *H pylori* could induce antibody production in response to antigens that crossreact against various platelet glycoprotein antigens. The possible role of CagA-positive strains as a pathogenic candidate for ITP was recognized in two molecular studies. The first showed a decline in platelet-associated immunoglobulin G in ITP patients after the eradication of *H pylori* infection as well as the existence of a molecular mimicry between those antibodies and the CagA protein.[17] The second study demonstrated that CagA antibodies cross-react with a peptide specifically expressed by platelets of patients with ITP.[18] This study, as well as supporting an association between CagA and ITP, also proposed a possible explanation for the fact that ITP may occur in only a small subset of patients infected by CagA-positive strains. In this regard, it should be noted that most Japanese *H pylori* strains are positive for CagA[19] and have the intact Cag pathogenicity island.[20] Further support to this hypothesis emerges from recent data of an Italian group, showing that the prevalence of the *H pylori* cagA gene was significantly higher in patients with ITP than in a control group.[21] Other putative targets of molecular mimicry are Lewis (Le) antigens, which are expressed by *H pylori* in a strain-specific manner. Le antigens adsorb to platelets and might serve as targets for anti-Le antibodies in patients with an appropriate genetic background.[22] Another hypothesis suggests that molecular mimicry of *cagA* or Lewis antigens and platelet antigens may initiate the development of ITP, but with time continued platelet destruction and epitope spreading may lead to the development of chronic thrombocytopenia refractory to eradication of *H pylori* infection.[23] This model is reminiscent of the role played by *H pylori* in the development of MALT lymphomas, which initially may respond to bacterium eradication but may subsequently develop new mutations leading to autonomous disease.

Recently, Semple and colleagues demonstrated that in the presence of antiplatelet antibodies, the LPS of Gram-negative bacteria can significantly enhance Fc-dependent platelet phagocytosis.[24] These results suggest that infectious agents in combination with antiplatelet antibodies could affect platelet destruction in vivo, which may be at least one explanation for why thrombocytopenia worsens in some patients with ITP during infections and, alternatively, resolves in other patients with ITP who are treated with bacterial eradication therapy.

Other studies have shown that some strains of *H pylori*

bind von Willebrand factor (VWF) and induce glycoprotein Ib (GPIb)– and FcRIIa-dependent platelet aggregation in the presence of *H pylori* antibodies.[25] Activation may promote platelet clearance and antigen presentation, which augments production of antibacterial antibodies. Somatic mutation may lead to the development of antibodies that either recognize bacterially derived factors that bind to platelets or crossreact with platelet antigens.[23]

Both *H pylori* infection and ITP are associated with a polarized Th1-type phenotype.[26,27] Accordingly, it may be speculated that *H pylori* infection creates an immunological environment that facilitates the onset and/or persistence of ITP.[28]

The last three hypotheses are not mutually exclusive and can account for the observation that clinical responses may occur as early as 1 week from initiation of eradication therapy, before antibody synthesis by plasma cells is affected.[29]

The importance of genetic factors emerged from the results of an Italian study, indicating that *H pylori*–positive patients had a lower frequency of DRB1*03 and higher frequencies of DRB1*11, DRB1*14, and DQB1*03 relative to *H pylori*–negative cases.[30] Confirmatory studies are needed to establish the clinical relevance of these findings.

Clinical Characteristics of *H Pylori*–Associated ITP

H pylori–infected ITP patients were found to be significantly older than *H pylori*–uninfected patients.[3,31] This is not unexpected, as the prevalence of *H pylori* infection in the general population increases with increasing with age.[1] In contrast, all prospective series that we reviewed failed to detect significant differences in other characteristics, such as sex and platelet count. A significant association between *H pylori* infection and the presence of symptoms of dyspepsia has been reported by Michel et al[6] but not by Stasi et al.[32] A cross-sectional study by Fukui et al did not find any correlation between *H pylori* infection and thrombocytopenia during pregnancy.[33] In a retrospective Japanese study, the *H pylori*–positive group was significantly older ($P < .005$) and had more cases of hyperplastic megakaryocytes in the bone marrow ($P = .01$) than patients without *H pylori* infection.[34]

Response to Eradication Therapy

An analysis of 25 reported series world-wide showed that eradication was successful in 671 of 792 (84.7%) patients.[9] In all studies cited in that systematic review eradication therapy consisted of the so-called "triple therapy," a combination of amoxicillin, clarithromycin, and a proton pump inhibitor usually given for 1 or 2 weeks. Of note, in most studies the mean platelet count was $> 30 \times 10^9$/L and relatively few patients with severe disease were investigated.

In the only Phase III trial, Suzuki et al evaluated the platelet count in a group of 25 *H pylori*-positive chronic ITP patients who were randomized to receive treatment or no treatment for *H pylori* infection.[35] Response to the treatment was defined as complete (CR) if the platelet count was above 150×10^9/L, and partial (PR) if the platelet count increased by more than 50×10^9/L 6 months after the eradication therapy. The investigators found that the eradication of *H pylori* infection in patients with ITP was associated with a platelet response: 46.2% in the eradication group (4 CR and 2 PR) and 0% in the non-eradication group ($P < .01$). The platelet response was also significantly more common in patients with infection sustained by CagA-positive strains of *H pylori* ($P = .04$). However, given the small number of patients recruited in the trial, these results should be interpreted with some caution.

The overall response of 24 Phase II trials with a total of 779 *H. pylori*-positive patients was 53%,[9] ranging from 0% in the North American series[6] to 100% in the early Italian series.[36] Two of these trials had an internal control. In the Italian-English study eradication therapy was administered to *H pylori*–positive patients who either had a platelet count $< 50 \times 10^9$/L or had symptoms of dyspepsia.[32] Platelet responses were observed in 17 of 52 (33%) patients who received treatment, and in 0 of 12 (0%) patients who did not receive treatment. Inaba et al administered 1-week triple therapy to 35 patients with chronic ITP.[37] A platelet response was observed in 11 (44%) of the 25 patients cured of *H pylori* infection, and in none of the 10 *H pylori*-negative patients ($P = .015$).

In the retrospective study by Fujimara et al a platelet response was observed in 63% of the successful eradication group.[34] Interestingly, an improvement of the platelet count was also observed in 15 (33%) of 46 *H pylori*–infected ITP patients who failed the eradication therapy. This finding could be explained in several ways, including an immunomodulatory effect of macrolides that is separated from the bacteriostatic effect.[38]

The uncertainties regarding the actual role of standard eradication therapy warranted a prospective study in which 37 ITP patients were treated with triple therapy irrespective of the presence or absence of *H pylori* infection.[29] With a therapeutic response defined as a platelet count $>100 \times 10^9$/L at 24 weeks, 16 of 26 *H pylori*–positive patients (62%) were responders, while none of the *H pylori*–negative patients was a responder. Besides, anti-GPIIb/IIIa antibody-producing B cells were significantly decreased at 12 and 24 weeks in *H pylori*–positive responders ($P < .0001$) and, to a lesser extent, in non-responders ($P = .02$), but not in *H pylori*–negative patients. This study clearly supports the notion that platelet recovery after *H pylori* eradication results from the disappearance of *H pylori* itself, rather than from other *H pylori*–independent mechanisms. It has been advanced that the increased platelet count in patients who failed the *H pylori* eradication or in those who received proton pump inhibitor monotherapy could have been mediated through a reduction in the quantity of *H pylori* and/or a bacteriostatic effect of the regimen.[39]

A small randomized study compared the treatment efficacy and benefit of *H pylori* standard eradication therapy with proton pump inhibitor monotherapy.[40] Of the 9 patients in the triple therapy arm 4 achieved a complete remission (CR) and 2 achieved a partial remission (PR); of the 8 patients in the monotherapy arm 3 achieved a CR and 2 achieved a PR.

The long-term results of *H pylori* eradication have been reported recently by an Italian group.[21] After a median follow-up of 60 months, a persistent platelet response was observed in 23 (68%) of 34 patients with eradicated infection; only 1 relapse occurred.

Adverse events from eradication therapy have been described as mild, usually consisting of abdominal pain and diarrhea, and lead to discontinuation of treatment in less than 5% of cases.

Predictors of Platelet Response to *H pylori* Eradication

The pretreatment factor that was more consistently associated with a platelet response to *H pylori* eradication was a shorter ITP duration.[32,34] Patients with very low platelet counts ($< 30 \times 10^9$/L) also appear to have fewer chances of response, although this issue has not been systematically addressed in most published reports. In the Italian/UK study, platelet responses were observed in 17 (33%) of 52 patients, but only 1 response was observed among patients with severe thrombocytopenia.[32] Other clinical features, such as age, sex, and previous therapies, including corticosteroids and splenectomy, were not useful to predict the platelet response. In one study, HLA-DQB1*03 haplotypes were shown to be associated with a higher probability of the platelet response, although the number of patients analyzed in that study was too small to draw conclusions.

As reported in the previous section, there is a significant discrepancy in the platelet response to eradication therapy among various countries. Cohorts from Japan and Italy had response rates of 39% to 100% in *H pylori*–infected ITP patients.[3,31] However, studies from Spain[41] and the United States[6,42] have documented little or no platelet response to triple therapy. Moreover, recent studies conducted in Serbia[43] and Turkey[44] showed a relatively low response rate (26% and 40%, respectively), whereas the single study from Colombia shows a very high and sustained response rate (80.8%).[9] Further analysis shows that in almost every series where there was a platelet response as a result of a successful eradication treatment, the *H pylori* infection rate in patients with ITP was relatively higher than in those where no association was found. So in the US, where the background prevalence of *H pylori* is low, there are also low chances of obtaining a platelet response to eradication therapy; in Japan, where the prevalence of *H pylori* in the general population is around 70%, eradication therapy produces platelet responses in a high proportion of cases. In this regard, it is noteworthy that the CagA positivity of *H pylori* varies depending upon geographic location. In Japan, most *H pylori* strains express CagA, whereas the proportion of CagA-positive strains in Western countries is lower.[45]

Conclusions

The data so far reported indicate that the prevalence of *H pylori* infection in ITP mirrors the prevalence of *H pylori* infection in the general population. Although the pathogenesis of ITP associated with *H pylori* is still not well defined, recent evidence suggests a plausible pathogenetic mechanism involving crossreactivity between platelet glycoproteins and the *H pylori* CagA protein.

The data indicate that eradication of *H pylori* is accompanied by a platelet response in approximately half of ITP adult patients, with ample variations in the response rate among the various series. The chances of response appear consistently high in patients from Italy and Japan, and have been reported very high in one study from Colombia. Responses are generally poor in the series from other countries. Bacterial factors (i.e., the variability of *H pylori* strains) may account for these findings. Eradication therapy has a favorable toxicity profile compared to standard ITP therapy. Should patients with ITP be routinely screened for *H pylori*? Considering the low costs, the noninvasiveness of diagnostic methods, and favorable toxicity profile of eradication therapy compared to standard ITP therapy, the detection and eradication of *H pylori* infection should be considered in those populations with a high background prevalence of *H pylori* infection.

What diagnostic tests for *H pylori* infection are preferable? Very sensitive, specific, and noninvasive diagnostic methods include the stool antigen test and the ^{13}C urea breath test.[2] The ^{13}C urea breath test has been recommended as a clinical gold standard against which other diagnostic methods can be validated. However, to avoid false negative results this test requires a patient to be off treatment with proton pump inhibitors for at least 2 weeks. If this is not possible, the stool antigen test is not available, and no other clinical indications for performing an endoscopy are present, a practical approach might involve screening patients with antibody assays and treating those patients who test positive.

Possible areas of research include (1) a comparison of antibodies to *H pylori*–associated antigens (CagA) in platelet eluates from ITP patients in countries with different prevalence of *H pylori* and different response rates to eradication therapy (e.g., Italy vs. Japan vs. US) and (2) the diagnosis and treatment of *H pylori* infection of all patients with newly diagnosed ITP before autonomous B-cell clones have developed.

Disclosures

Conflict-of-interest disclosure: R.S. declares no competing financial interests. D.P. is a consultant for Amgen, is on their speakers bureau, and receives research funding and honoraria from them; he receives research funding and honoraria from Baxter; and has equity ownership in and receives research funding and honoraria from GSK.
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